year: rather it cumulatively lowers the ability of the hospital and community services to meet health care needs.[2]

On the capital side the hospital and community services are to receive an extra £89m (11% extra), taking their provision to £921m. The government estimates that land and other estate sales will raise another £280m, bringing total capital spending to just over £1·2 billion. As with revenue, money raised by health authorities—in this case from the once and for all sale of land and buildings—makes the most important contribution to financial growth. The supply of salable NHS land is, however, strictly limited and will not provide an inexhaustible supply of cash. Inflation at 6% would reduce the capital allocation increase to about £300m, and yet the Public Accounts Committee has estimated that some £2 billion is needed just to bring existing hospitals up to standard.[3]

The family practitioner services will receive an increase of £280m next year, 6·6% above this year's estimated spending. Inflation at 6% will reduce this to a real increase of just £2·6m (0·6%). Yet again it is savings in the form of reduced superannuation contributions of £40m that recover the budget. The resulting real increase of 1·6% is, however, the lowest since 1981-2 apart from that in 1985-6.

JOHN APPLEBY

Economic Correspondent, *BMJ*

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Regular Review

Anticoagulants in venous thromboembolism

Guidelines for optimum treatment

Recommendations

Our own regimen for treating patients with venous thromboembolic disease is to give heparin by intravenous infusion to maintain the kaolin cephalin clotting time between 1·5 and 2·5 times the control values according to table I. Heparin is normally continued for five days. The kaolin cephalin clotting time is best measured at the same time of day because of the diurnal variation.[3] Warfarin is started on the third day with the aim of maintaining an international normalised ratio between 2·0 and 2·5. Once the predicted dose is given, according to figure 1, the patient may be discharged with regular follow up for the first month. Warfarin is given for four weeks (or longer if there are persisting risk factors). A patient with a single recurrence is treated for three months, whereas those patients with repeated thromboembolic episodes are considered for longer treatment (sometimes life long).

Opinions differ widely on how best to use heparin and warfarin to treat deep vein thrombosis and pulmonary embolism. We aim here to give clear guidelines (see box and table I), but the toxicity of these anticoagulants makes it important to confirm the diagnosis of thromboembolism objectively whenever possible.[1,2]

Heparin

Because of its immediate action heparin is usually the anticoagulant to be used first in venous thromboembolism. It should be given as an intravenous infusion to maintain the heparin activity—as measured by the activated partial thromboplastin time or its equivalent (for example, the kaolin cephalin clotting time)—at 1·5-2·5 times the control value. This therapeutic range was initially based on animal work, which showed that the clot was unlikely to extend if the activated partial thromboplastin time was kept at above 1·5 times the control value.[4] Studies in humans have supported this view,[5,6] and venous thrombosis may recur in patients whose blood has been insufficiently anticoagulated with heparin for as little as 24 hours early in the course of treatment.[6]

Heparin was the commonest cause of drug related death in one study of fit hospital patients.[7] The incidence of haemorrhage may be directly related to the intensity of heparin anticoagulation: the incidence of haemorrhage is increased eightfold if the activated partial thromboplastin time is more than three times the control.[8] Especially in the early period of treatment the activated partial thromboplastin time must be at least 1·5 times the control value to prevent recurrence but less than 2·5 times the control to reduce the risk of haemorrhage.

The ideal activated partial thromboplastin time is not readily achieved: the blood of many patients was insufficiently anticoagulated for a long time in one hospital audit.[9] It is difficult to estimate heparin requirements, but guidelines derived from the non-linear dose-response relation may

TABLE I—*General guidelines for a regimen of anticoagulant treatment*

Day	Action
1-5 (inclusive)	Check baseline KCCT and INR before treatment. Heparin infusion: give loading dose of 5000 units followed by heparin infusion of 1400 units/hour. Check KCCT after 4-6 hours of infusion and daily thereafter, adjusting infusion rate to keep the time 1·5-2·5 times the control
3 (5 pm)	Induction dose of warfarin 10 mg
4 (9-10 am)	Send blood for KCCT and INR
(5 pm)	Warfarin as for day 4 INR*
5 (9-10 am)	Send blood for KCCT and INR
(5 pm)	Warfarin as for day 5 INR*
6 (9-10 am)	Send blood for day 6 INR. Suggested maintenance dose of warfarin will depend on this result
(5 pm)	Warfarin as for day 6 INR (this is projected maintenance dose)
7 onwards	INR taken as usual and warfarin dose adjusted accordingly

KCCT = Kaolin cephalin clotting time.
INR = International normalised ratio.
*See table II.

appreciably improve control, particularly for those whose blood would otherwise be insufficiently anticoagulated (fig 1).[10]

Intravenous infusion is the best way to give heparin. It is associated with fewer haemorrhagic episodes than bolus delivery.[11-13] There is increasing interest in full anticoagulation using subcutaneous calcium heparin, but published results comparing intravenous infusion of heparin with subcutaneous heparin reach opposite conclusions—possibly because the values of activated partial thromboplastin time achieved in each treatment group have not been comparable.[6 14-17] Treatment fails because therapeutic concentrations are not achieved early, but if this problem can be overcome the subcutaneous route may prove a satisfactory alternative. The calcium salt seems to cause less pain than the sodium salt when given subcutaneously.[18]

Venous thrombus takes about 10 days to organise, and it is often argued that heparin should be continued for at least this long. This policy assumes that heparin is a better anticoagulant than warfarin, a view based largely on animal experiments.[4 19] The only prospective clinical study to look into this problem suggested that long periods of heparin treatment were not necessary.[20] A total of 226 patients with well diagnosed venous thromboembolic disease were randomised to start taking warfarin after either one or seven days' treatment with heparin; heparin was discontinued as soon as a therapeutic international normalised ratio was achieved. There was no significant difference in recurrence after three to six months of follow up.

Heparin schedule

(1) Loading dose: 5000 U over 5 minutes

(2) Infusion: start at 1400 U/hour—for example, 8400 U in 100 ml over six hours

(3) Check KCCT after six hours. Adjust dose according to ratio of KCCT to control value (KCCT ratio) as follows:

KCCT ratio	*Change in infusion rate*
>7	Stop temporarily and reduce dose by >500 U/hour
5·1-7·0	Reduce by 500 U/hour
4·1-5·0	Reduce by 300 U/hour
3·1-4·0	Reduce by 100 U/hour
2·6-3·0	Reduce by 50 U/hour
1·5-2·5	No change
1·2-1·4	Increase by 200 U/hour
<1·2	Increase by 400 U/hour

(4) Wait 10 hours before next KCCT estimation unless KCCT ratio is >5·0, in which case more frequent estimation—for example, four hourly—is advised

FIG 1—*Heparin schedule according to kaolin cephalin clotting time ratio (KCCT ratio), which should be measured if possible between 9 am and noon. These guidelines were drawn up using a platelet substitute (Diagen; Bell and Alton); local validation will be necessary*

TABLE II—*Warfarin schedule*

Day	KCCT (9-10 am)	Heparin dose	INR (9-10 am)	Warfarin dose given at 5 pm (mg)
1	1·5-2·5 × control	As for KCCT	—	0
2	1·5-2·5 × control	As for KCCT	—	0
3	1·5-2·5 × control	As for KCCT	<1·4	10
4	1·5-2·5 × control	As for KCCT	<1·8	10
			1·8	1
			>1·8	0·5
5	1·5-2·5 × control	As for KCCT. Stop heparin after dose on day 5	<2·0	10
			2·0-2·1	5
			2·2-2·3	4·5
			2·4-2·5	4
			2·6-2·7	3·5
			2·8-2·9	3
			3·0-3·1	2·5
			3·2-3·3	2
			3·4	1·5
			3·5	1
			3·6-4·0	0·5
			>4·0	0
6	—	—		*Predicted maintenance dose:*
			<1·4	> 8
			1·4	8
			1·5	7·5
			1·6-1·7	7
			1·8	6·5
			1·9	6
			2·0-2·1	5·5
			2·2-2·3	5
			2·4-2·6	4·5
			2·7-3·0	4
			3·1-3·5	3·5
			3·6-4·0	3
			4·1-4·5	Miss out next day's dose then give 2 mg
			>4·5	Miss out two days' doses then give 1 mg

(1) KCCT should be within or below therapeutic range (1·5-2·5 times control). If KCCT is above this range the heparin effect on INR is neutralised with protamine (0·4 μg/ml plasma) added to the sample by the haematologist.
(2) If heparin treatment is not being given start the schedule at day 3.
(3) Special care should be taken with patients with heart failure or liver disease and with those immediately after an operation as their sensitivity to warfarin may vary with time.
(4) If INR on day 6 is <2·0 heparin may be given again until the INR is within the desired range.
(5) If the INR on day 3 is ≥1·4 the initial dose of warfarin should be reduced and the schedule is no longer relevant.

Since the cumulative incidence of haemorrhage is greater in patients having heparin than in those having warfarin[8] a short period of heparin treatment should be associated with a lower risk of bleeding. It should also be cheaper as treatment with heparin normally requires inpatient care. Many doctors are unwilling to give patients with severe thrombotic disease only three to four days' heparin, and as such patients were generally excluded from the prospective study[20] longer periods of heparin treatment may be justified for these patients. There is, however, a risk of life threatening heparin induced thrombocytopenia after seven days of treatment with heparin.[21] Shorter periods of treatment may thus give an optimal ratio of risk to benefit.

Warfarin

Oral anticoagulants prevent extension and embolisation of venous thrombi.[22 23] Their effectiveness is measured by the international normalised ratio, which expresses the prothrombin time using a world standard for thromboplastin reagents.[24] An international normalised ratio between 2·0 and 2·5 prevents recurrence of venous thromboembolism as effectively as more intense treatment.[25] The incidence of haemorrhage is related to the prothrombin time in a log linear way[26] so the international normalised ratio should be maintained as close to the recommended range as possible. A regimen has been described for starting warfarin treatment safely with a variable induction dose[27]: it takes into account the considerable variability among patients in response to the drug and predicts the maintenance dose after three doses (table II). The method is possible because the international normalised ratio may be reliably measured while the patient is taking heparin,[28] unless the activated partial thromboplastin time is more than 2·5 times the control, when the heparin activity of the plasma sample should be neutralised in vitro with protamine. Patients may be discharged once the predicted dose has been given, but they should be followed up regularly for the first month. They should be given clear advice on the dos and don'ts of anticoagulant treatment; written information, particularly on the risks of drug interactions, is given on the cards available from the Department of Health for patients being treated with anticoagulants. Follow up is ideally performed in a specialist anticoagulant clinic.

Recommendations on the optimum duration of oral anti-

coagulation for patients with venous thromboembolism range from three weeks to six months.[29 30] The confusion is caused mainly by the absence of adequate clinical trials. A retrospective study by Coon and Willis[31] may have had undue influence on treatment over the past decade—despite being reasonably criticised.[32] The study looked at recurrence rates for venous thromboembolism in a widely diverse group of 1539 patients over 25 years. The risk of recurrence after discharge from hospital fell exponentially and levelled off at around 14 weeks. This led to the recommendation that warfarin should be continued for a minimum of four months. Among those patients with a first episode who actually received prophylactic oral anticoagulation after hospital discharge (as distinct from those who received only a short period of inpatient treatment) the risk of recurrence levelled off at about four weeks (fig 2).

A more recent retrospective study of 370 patients (in whom the original diagnosis and the recurrence were well described) found that the treatment with warfarin for up to six weeks did not carry a higher risk of recurrence than treatment for seven to 27 weeks or even longer.[33] Two prospective studies also supported the view that a maximum of six weeks' treatment is enough for patients with no persisting risk factors.[34-36] O'Sullivan randomised 186 patients with deep venous thrombosis or pulmonary embolism to receive warfarin for six weeks or six months and found a similar (7% and 10%, respectively) recurrence rate in each group after a minimum follow up of 12 months.[34] In an unstated proportion of patients the diagnosis was not, however, adequate and it is not clear if the duration of follow up was the same for each group. A similar study of treatment for three or six weeks also failed to make an objective diagnosis in 46% of the patients.[35] A more closely controlled study of 135 patients with well diagnosed proximal vein thrombosis compared warfarin treatment for one and six months and found no difference in recurrence rate (16% and 17%, respectively).[36]

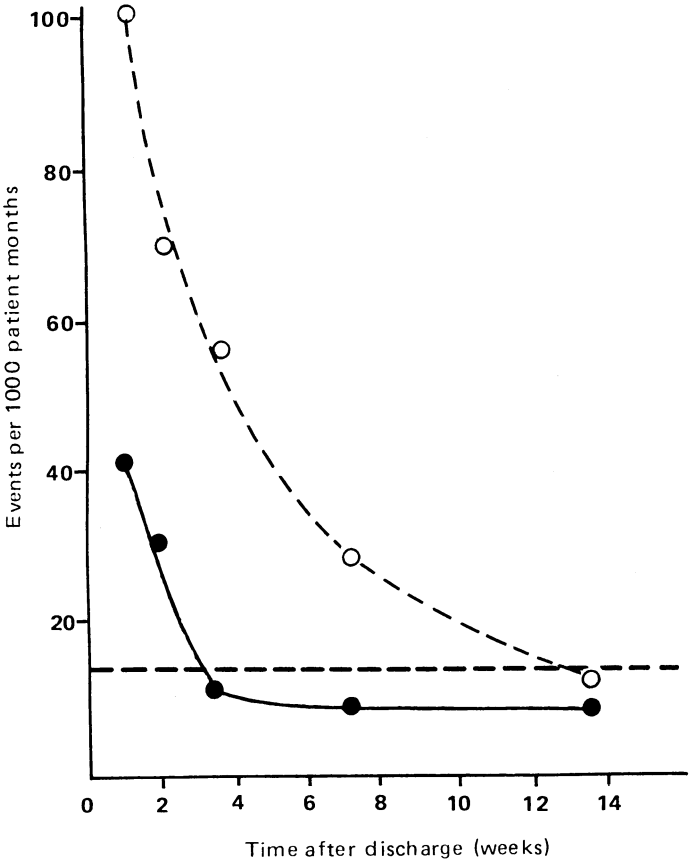

FIG 2—*Rates of recurrence of thromboembolism and major haemorrhage after venous thromboembolism for patients with a history of previous thromboembolism (○) and for those with a first episode who had received some anticoagulant treatment after discharge (●). The horizontal dotted line shows the incidence of major haemorrhage if the international normalised ratio is 2. Data from Coon and Willis[31] and Levine et al[37]*

Analysing the pooled data from these two most comparable studies, we find that the recurrence rate is about 1·5% less in those given short rather than long courses of treatment.[34 36] The 95% confidence limits are, however, wide, and short course treatment might give a recurrence rate 9% lower or long course treatment might give a rate 5% lower. A larger multicentre study of treatment for four weeks or three months is being performed by the British Thoracic Society and should provide further information.

Recurrence rates are not the only factors to be considered when deciding on the duration of anticoagulation. Warfarin may cause haemorrhage, and in a study of 47 patients with an international normalised ratio maintained at 2 the incidence of major haemorrhage was 14 for every 1000 patient months.[25] Figure 2 shows that the risk of major haemorrhage becomes greater than the risk of recurrence after about three weeks of treatment. In an analysis of three carefully randomised studies of anticoagulant prophylaxis in venous thromboembolism[37] in 110 patients with an international normalised ratio between 2 and 4·5 (higher than the currently recommended range) the average incidence of major haemorrhage was 22 for every 1000 patient months. These data suggest that a maximum of four weeks' treatment with warfarin may have the best ratio of risk to benefit in treating a first episode of venous thromboembolic disease.

There is little information available on how long to continue treatment in patients with recurrent episodes. Analysis of the data of Coon and Willis suggests that the risk of recurrence in patients with more than one episode of thromboembolic disease equals the risk of major haemorrhage at around 12 weeks (fig 2).[21] It is not possible from their data to separate those who had received prophylactic anticoagulation as outpatients from those who received anticoagulants only during their hospital stay, and in those given anticoagulants as outpatients the incidence of recurrent embolism may have fallen faster. We recommend that three months' treatment should be adequate for patients with a repeat thromboembolic event. Lifelong treatment may be considered in patients with repeated episodes or with a continuing risk factor—for example, a malignancy or antithrombin III deficiency.

Further research

Although thrombolytic agents clear emboli in pulmonary arteries more rapidly than anticoagulants,[38] they have not been shown to reduce mortality. They are generally reserved for life threatening massive pulmonary embolism.[39]

Plasminogen activators more specific for fibrin than streptokinase are now available for patients with severe haemodynamic disturbance, but few trials of their value in venous thromboembolism have been published.[40] But even if they are safe and effective they are likely to be costly, and heparin and warfarin will continue to be important in managing venous thromboembolism for many years to come.

A FENNERTY
Senior Registrar

I A CAMPBELL
Consultant Physician

Department of Thoracic Medicine,
University of Wales College of Medicine,
Llandough Hospital,
Penarth, South Glamorgan

P A ROUTLEDGE

Reader in Clinical Pharmacology,
Department of Pharmacology and Therapeutics,
University of Wales College of Medicine,
Cardiff CF4 4XN

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Correction

Aspirin for strokes and transient ischaemic attacks

An author's error occurred in Dr Peter Sandercock's editorial (22 October, p 995). In the third sentence of the penultimate paragraph the dose of aspirin being tested in the Swedish low dose aspirin trial is 75 mg, not 30 mg as published.

INSTRUCTIONS TO AUTHORS

The BMJ has agreed to accept manuscripts prepared in accordance with the Vancouver style (BMJ, 6 February 1988, p 401) and will consider any paper that conforms to the style. More detailed and specific instructions are given below.

The following include the minimum requirements for manuscripts submitted for publication.

All material submitted for publication is assumed to be submitted exclusively to the *BMJ* unless the contrary is stated.

Manuscripts will be acknowledged; letters will not be unless a stamped addressed envelope is enclosed.

Papers will normally be refereed and may be statistically assessed before acceptance.

Authors should give their names and initials, their posts at the time they did the work, and one degree or diploma. All authors must sign their consent to publication.

Three copies should be submitted. If the manuscript is rejected these will be shredded.

Typing should be on one side of the paper, with double spacing between the lines and 5 cm margins at the top and left hand side of the sheet.

Abbreviations should not be used in the text.

Drugs should be given their approved names, not their proprietary names, and the source of any new or experimental preparations should be given.

SI units are used for scientific measurements, but blood pressure should continue to be expressed in mm Hg.

Statistical procedures should be described in the methods section or supported by references.

Tables and illustrations should be separate from the text of the paper. Tables should be simple and should not duplicate information in the text of the article.

Photographs should be trimmed to remove all redundant areas and should be no larger than 30×21 cm (A4); the top should be marked on the back of each print.

Abstracts should accompany all original articles. They should be up to 150 words long and should set out what was done, the principal findings, and their implications.

References must be in the Vancouver style and their accuracy checked before submission. They should be numbered in the order in which they appear in the text. Each reference should include the names and initials of each author (or, if more than six, the first three followed by *et al*), the title of the article, the title of the journal (abbreviated according to the style of *Index Medicus*), the year, the volume, and the first and last page numbers. References to books should give the names of any editors, the place of publication, the publisher, and the year.

Letters to the editor submitted for publication must be signed personally by all authors, who should include one degree or diploma.

The editor reserves the customary right to style and if necessary shorten material accepted for publication and to determine the priority and time of publication.

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